Articles

Neurobehavioral Presentations of Brain Neoplasms

CHRISTOPHER M. FILLEY, MD, *and* BETTE K. KLEINSCHMIDT-DeMASTERS, MD, *Denver, Colorado*

We studied 8 patients with frontal or temporolimbic neoplasms who had psychiatric presentations to clarify diagnostic criteria for distinguishing psychiatric disease from structural brain lesions and to examine brain-behavior relationships associated with cerebral neoplasms using modern neuroimaging techniques. Medical records were retrospectively reviewed for evidence of neurobehavioral and neurologic manifestations, tumor histologic features, and the results of treatment. Clinical presentations were correlated with tumor location as determined by computed tomography and magnetic resonance imaging. Patients with frontal lobe tumors presented with abulia, personality change, or depression, whereas those with temporolimbic tumors had auditory and visual hallucinations, mania, panic attacks, or amnesia. After treatment, neurobehavioral syndromes abated or resolved in 7 of 8 patients. We recommend that any patient 40 years of age or older with a change in mental state, cognitive or emotional, should have neuroimaging of the brain. Any patient with a psychiatric presentation who has specific neurobehavioral or neurologic findings or an unexpectedly poor response to psychopharmacologic treatment should also have brain imaging. These case reports extend and update observations on the importance of frontal and temporolimbic systems in the pathogenesis of neurobehavioral disorders.

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Whereas patients with brain neoplasms characteristically have focal neurologic disturbances, it was well recognized before neuroimaging became available that some tumors manifest with neurobehavioral or psychiatric features.[1-7] Conversely, only a small percentage (3%) of institutionalized psychiatric patients have intracranial tumors.[8,9] Because the number of psychiatric patients who have brain tumors is relatively small, it is a matter of debate among psychiatrists and neurologists whether all patients with newly recognized psychiatric symptoms should undergo neuroimaging studies. This issue was reviewed with regard to computed tomography (CT) a decade ago.[10] Since then, magnetic resonance imaging (MRI) has become widely available, and little information has appeared on the utility of MRI in this setting. Nevertheless, most clinicians advocate CT or MRI scanning in older patients with a new occurrence of neurobehavioral symptoms or signs and patients of any age who have these features accompanied by headache, nausea and vomiting, papilledema, seizures, or focal deficits.

Despite this general consensus, patients with brain tumors may still mistakenly carry a diagnosis of primary psychiatric disorder months or years before the discovery of tumor. Since 1987 we have seen eight patients at our institution with frontal or temporolimbic tumors who had psychiatric symptoms for months or years before thorough evaluations detected brain neoplasms. All patients with low-grade, benign, or excisable neoplasms (7 of 8) were substantially improved or cured after surgical treatment, emphasizing the importance of a correct diagnosis. Modern detailed neuroimaging studies allow a useful correlation between tumor location and clinical presentation. These cases are of interest in light of recent advances in the understanding of brain-behavior relationships.

Method

This was a retrospective study of patients seen at our institution since 1987 who had psychiatric presentations that were later attributed to a brain neoplasm. Cases were identified after brain tissue specimens were submitted for neuropathologic diagnosis. One of us reviewed all patients' medical records in detail (C.M.F.) or determined their tumor histology (B.K.K.). All CT and MRI scans were reviewed, and tumor locations were correlated with clinical presentations.

From the Departments of Neurology (Dr Filley) and Pathology and Psychiatry (Dr Kleinschmidt-DeMasters), University of Colorado Health Sciences Center (UCHSC) and the Denver Veterans Affairs Medical Center, Denver.
Reprint requests to Christopher M. Filley, MD, Behavioral Neurology Section, UCHSC B183, 4200 E Ninth Ave, Denver, CO 80262-0813.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CT = computed tomography
MRI = magnetic resonance imaging
PET = positron emission tomography

Report of Cases

Patient 1. This 56-year-old right-handed homemaker had progressive apathy, social withdrawal, and poor self-care for three years and was admitted to a psychiatric facility for depression. Because she was unresponsive to appropriate antidepressant medications, a CT scan was taken of the head. This study revealed an enhancing, 8-cm, medial bifrontal mass (Figure 1). Total excision of a benign transitional-type meningioma led to rapid and dramatic improvement, and four months after the operation she was animated, cheerful, and motivated to resume her previous life.

Patient 2. This 63-year-old left-handed taxi driver sought care because for five weeks, in a departure from his previous personality, he had been apathetic and irritable and two weeks before admission right hemiparesis and anomia had developed. A CT scan disclosed a 3 × 4 cm enhancing lesion involving the left medial frontal lobe, the genu of the corpus callosum, and the right medial frontal lobe (Figure 2). Small stereotactic biopsies revealed a malignant small-cell neoplasm that could not be further characterized by immunohistochemistry studies, and treatment with cranial irradiation and carmustine (formerly BCNU) was instituted. Two months after discharge, his personality change had resolved considerably, and a CT scan showed dramatic resolution of the mass lesion after therapy, most consistent with a primary malignant lymphoma of the central nervous system (CNS). He died ten months later of respiratory distress and sepsis, and an unsuspected adenocarcinoma of the cecum was found. The brain showed multifocal, ill-defined infiltrates of malignant immunoblastic lymphoma around blood vessels and in periventricular and leptomeningeal sites.

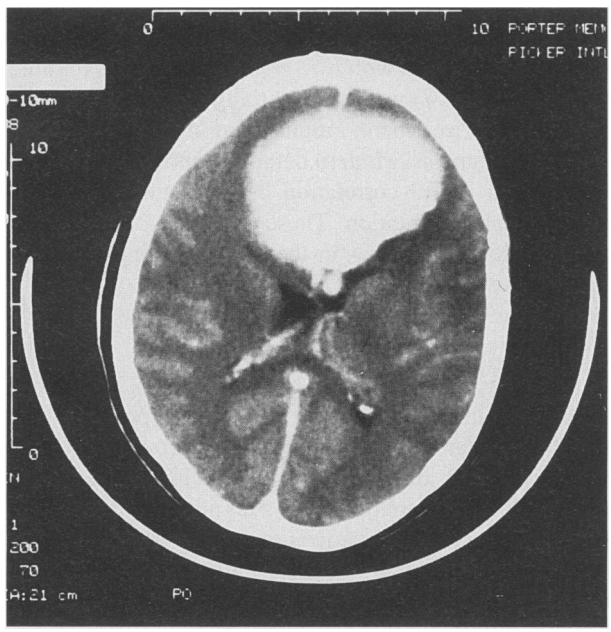

Figure 1.—*Frontal lobe tumor.* Patient 1 had abulia due to a benign meningioma. A computed tomographic scan shows severe compromise of both medial frontal lobes. Note the homogeneous enhancement in the 8-cm mass.

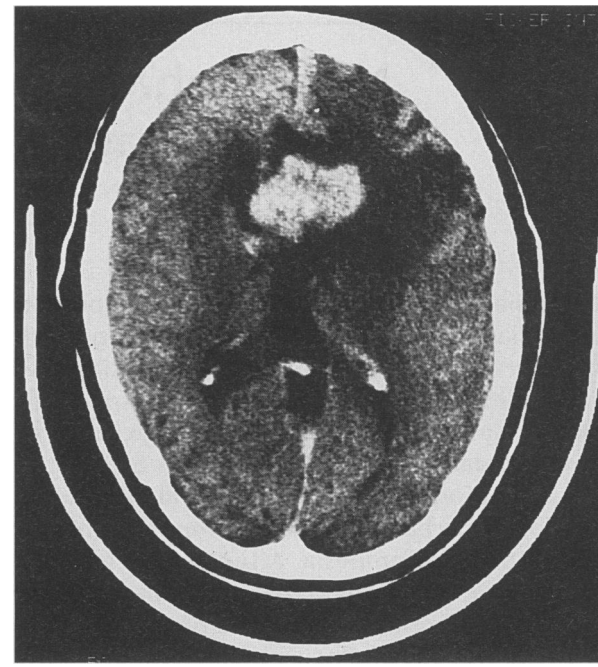

Figure 2.—*Frontal lobe tumor.* Patient 2 presented with personality change from his lymphoma that involved both medial frontal lobes and crossed the corpus callosum, as seen on this enhanced computed tomographic scan. Extensive low-density edema surrounds the tumor.

Patient 3. This 53-year-old left-handed postal worker for the past 18 months had had profound depression and a 27-kg (60-lb) weight loss before left hemiparesis was noted. A T1-weighted MRI scan showed a 3-cm enhancing mass lesion in the anterior right frontal lobe (Figure 3). Further evaluation revealed a mass in the left lower lobe of the lung, and excision of the brain tumor led to a diagnosis of moderately differentiated, metastatic squamous cell carcinoma. After the operation, the patient reported substantial lessening of his depressive symptoms and only mild residual hemiparesis.

Patient 4. After two months of auditory hallucinations, this 22-year-old right-handed mechanic was admitted to a psychiatric hospital. Memory and word-finding problems were then noted, and he was found on CT and T2-weighted MRI to have a 2-cm, nonenhancing, left medial temporal mass (Figure 4). Total excision of this lesion, which required two procedures, showed it to be a low-grade oligoastrocytoma, grade 1 of 4. Although he had been treated with haloperidol for hallucinations, tumor resection led to lessening of his symp-

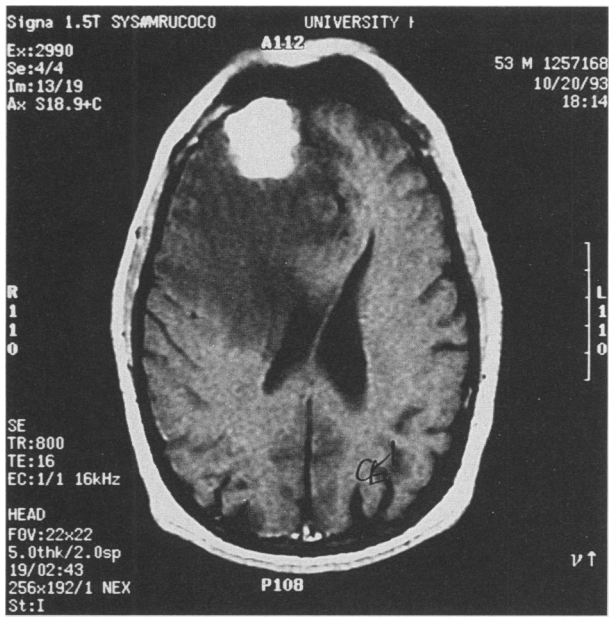

Figure 3.—*Frontal lobe tumor.* Patient 3 was profoundly depressed preoperatively, but after surgical removal of his enhancing 3-cm right frontal pole metastasis, he was greatly improved. The large area of surrounding edema on this enhanced T1-weighted magnetic resonance imaging scan further compromised the right frontal lobe and added to his neurobehavioral deficit (TR = 800 msec, TE = 16 msec).

toms, and the drug was no longer required. Follow-up at two years revealed no hallucinations and no tumor recurrence.

Patient 5. This 31-year-old right-handed laborer was admitted to a psychiatric hospital with auditory and visual hallucinations. The neurologic examination disclosed left hemiparesis, and neuroimaging studies (CT, MRI, and angiography) revealed a 6-cm tumor in the right temporal lobe, with massive edema extending into the frontal and parietal lobes (Figure 5). Surgical excision showed the lesion to be an oligodendroglioma, grade 2 of 4. The patient subsequently showed improvement in his psychosis, but had recurrence of the tumor, necessitating reoperation. After several debulking procedures, he eventually died; no autopsy was performed.

Patient 6. After a 20-year history of intermittent depression, this 56-year-old right-handed homemaker had a new onset of disorganized thinking, flight of ideas, and pressured speech three months before admission to a psychiatric hospital for mania. An MRI scan revealed a butterfly lesion involving 3-cm masses in both temporal lobes and tumor in the corpus callosum and the fornix (Figure 6). Biopsy disclosed a glioblastoma multiforme. Three weeks later, she had a perforated duodenal ulcer necessitating emergent surgical intervention and a Billroth II procedure, then lapsed into stupor and coma, dying a month after the initial diagnosis. An autopsy showed a large subdiaphragmatic abscess from duodenal perforation and amyloid deposits in the spleen and adrenal glands, with a normal bone marrow. The glioblastoma multiforme infiltrated the limbic system, including the left hippocampus and amygdala, the hypothalamus, the fornices, and the right hippocampus and amygdala. The posterior thalami, septum pellucidum, and deep right parietal lobe were also involved.

Patient 7. Two months after the onset of panic attacks, characterized by episodic fear, dyspnea, lower extremity paresthesias, diaphoresis, and tremulousness, this 56-year-old right-handed farmer was found on MRI scan to have a 5 × 4 cm pituitary mass extending into the left medial temporal lobe and thalamus; in addition, the lesion compressed the right medial temporal lobe (Figure 7). The patient underwent two procedures to reduce this weak gonadotropic cell pituitary adenoma to 10% of its original size, with a greater debulking of the tumor on the right side and more decompression of the right than the left temporal lobe. After the second operation, his panic attacks completely resolved.

Patient 8. This 45-year-old right-handed secretary had dysfunction of her recent memory for 12 months before admission. The family noted apathy and poor motivation, and she was seen by a psychiatrist who diagnosed depression. Neurologic examination, however, disclosed amnesia and a subtle bitemporal hemianopia, prompting an MRI scan. A 6 × 3 × 3 cm suprasellar mass was found that extended upward into the thalami and displaced the forniceal columns (Figure 8). After two transsphenoidal procedures that resulted in partial resection of this weak gonadotropic cell pituitary adenoma, her memory improved substantially.

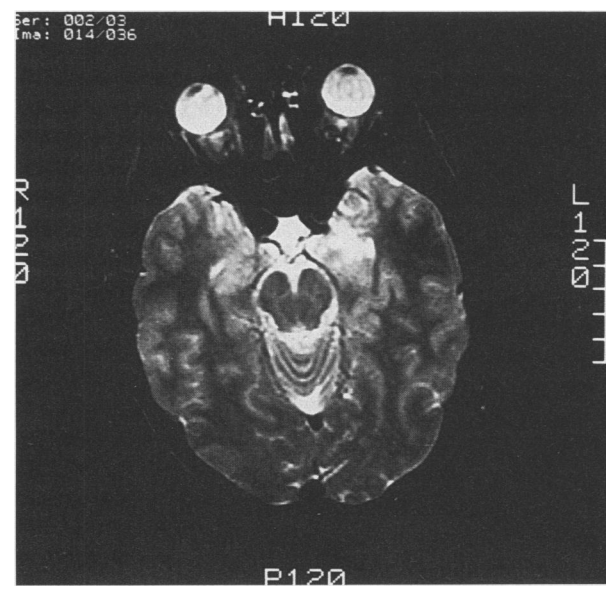

Figure 4.—*Temporolimbic tumor.* Patient 4 had auditory hallucinations for 2 months before the removal of a low-grade left temporal lobe oligoastrocytoma. The small 2-cm lesion shows increased signal intensity on this T2-weighted magnetic resonance imaging scan (TR = 2.0 sec, TE = 80 msec).

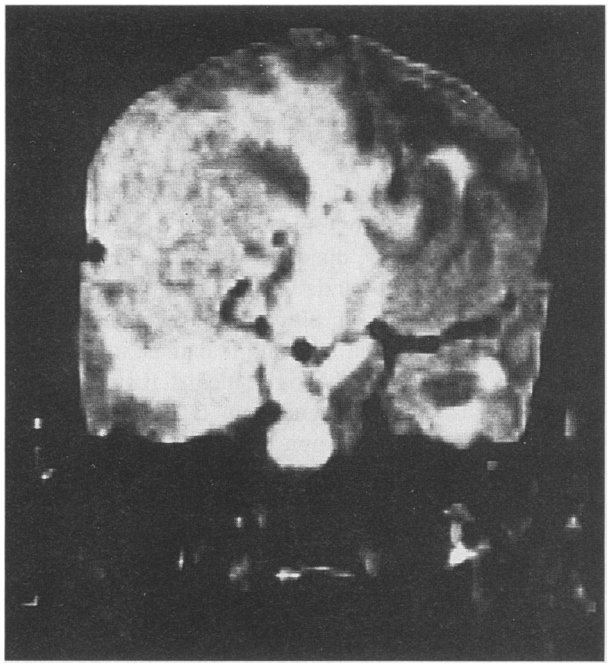

Figure 5.—*Temporolimbic tumor.* Patient 5 had auditory and visual hallucinations from presumed primary psychiatric disease for an indefinite length of time before being studied radiologically. This T2-weighted coronal magnetic resonance imaging scan, hampered by movement artifact, shows the massive right temporolimbic oligodendroglioma with additional high signal intensity in the frontoparietal areas thought to represent edema (TR = 3.0 sec, TE = 40 msec).

Summary of Cases

These eight cases represent a broad spectrum of intracranial neoplasms: one glioblastoma multiforme, one primary CNS malignant immunoblastic lymphoma, one oligoastrocytoma, one oligodendroglioma, one meningioma, two pituitary adenomas, and one metastatic lung carcinoma. Although the type of neoplasm varied, each was primarily located in frontal or temporolimbic areas. All the patients presented with symptoms and signs of neurobehavioral involvement that led to the consideration of primary psychiatric disorders (Table 1). Detailed neuropsychological testing had not been done preoperatively on any patient.

All patients with low-grade, benign, or excisable neoplasms were greatly improved or cured after surgical intervention and tumor resection (patients 1, 3, 4, 7, 8). One patient with a glioblastoma multiforme (patient 6) died rapidly, and one with primary CNS lymphoma improved temporarily with intensive irradiation, chemotherapy, and lesion reduction but died ten months later of systemic causes (patient 2). The oligodendroglioma of patient 5 was far advanced by the time a correct diagnosis was obtained, although surgical debulking did effect considerable clinical improvement.

These cases all suggest that the neoplasm was the actual cause of the neurobehavioral dysfunction. Table 1 divides the cases into those with frontal and those with

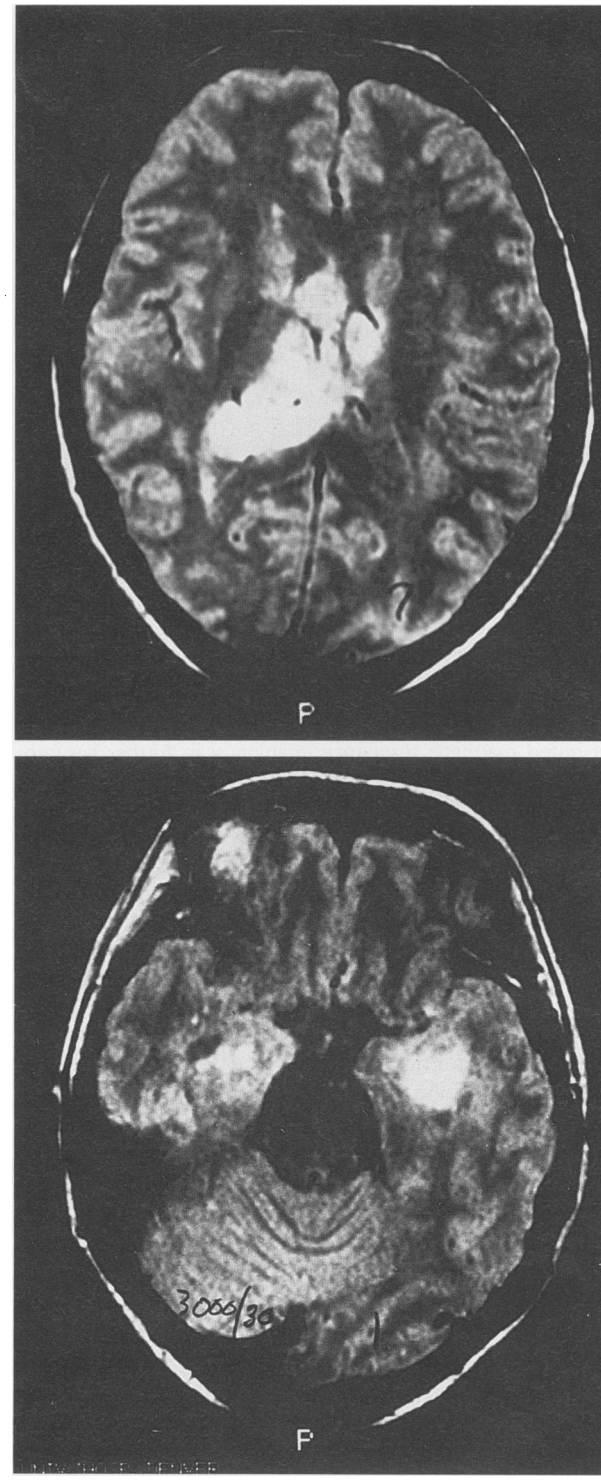

Figure 6.—*Temporolimbic tumor.* Patient 6 was manic for 3 months, and her age prompted this first echo T2-weighted magnetic resonance imaging scan showing bilateral medial temporal involvement with glioblastoma multiforme (TR = 3.0 sec, TE = 30 msec). **Top,** The tumor is shown in the forniceal columns and right posterior temporal lobe. **Bottom,** More left-sided anterior temporal lobe involvement is shown. The patient died soon thereafter, and autopsy revealed diffuse infiltration of the temporal lobes, forniceal columns, thalami, and hypothalami by glioblastoma multiforme.

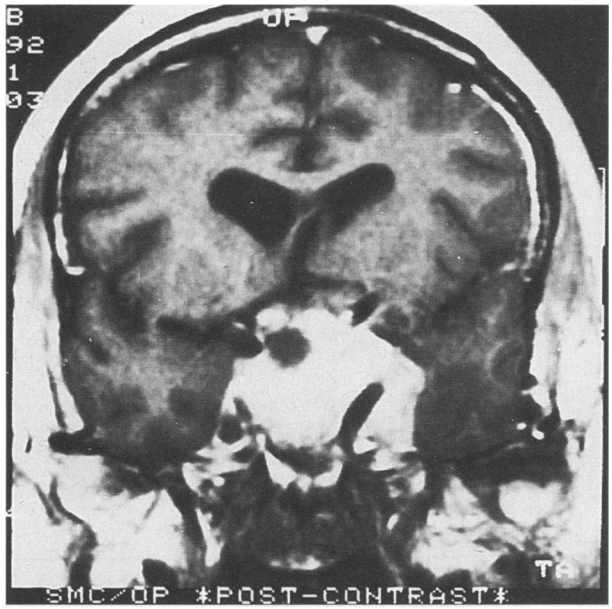

Figure 7.—*Temporolimbic tumor.* Patient 7 had 2 months of panic attacks, and this T1-weighted, enhanced coronal magnetic resonance image shows a pituitary macroadenoma extending into the left temporal lobe and thalamus and compressing the right medial temporal lobe (TR = 45 msec, TE = 15 msec). Debulking eliminated the panic attacks.

temporolimbic sites of origin, and all the presentations in both groups can be associated with damage or dysfunction in the specific areas involved. Although psychiatric diagnoses were considered in all patients, careful attention to neurobehavioral and neurologic aspects of these cases resulted in accurate diagnoses and appropriate therapy.

Discussion

Diagnostic Considerations

Classic neurologic symptoms and signs may be minimal or absent in patients with brain neoplasms, and even large tumors, because of a slow growth rate, may escape detection. Medial frontal lobe or periventricular midline nonobstructive tumors may also present with subtle, nonfocal abnormalities. Before CT and MRI scanning were available, many such cases in psychiatric settings were undiagnosed,[8] and it seems probable that some still go undetected. With the availability of CT and particularly MRI, however, the likelihood of finding tumors is much greater, and the cost of neuroimaging procedures is outweighed by the possibility of failing to detect surgically accessible lesions. Benign tumors such as meningiomas and pituitary adenomas may be curable by surgical therapy alone.

Patients with psychiatric presentations usually have psychiatric disorders, but the possibility of a neurobehavioral syndrome due to a structural lesion should be considered. Brain tumors can be suspected in particular because of their typically insidious onset, and they often present with recognizable neurobehavioral dysfunction. Although formal mental state examination is crucial, the distinction of patients with neoplastic brain lesions from those with primary psychiatric illnesses can be problematic. Psychiatrists and neurologists well recognize that brain tumors cannot always be detected by attention to neurobehavioral features. Nevertheless, detailed mental state testing combined with the traditional neurologic examination will clearly uncover more cases of these potentially reversible lesions. Neuropsychological assessment can also contribute useful information.

The question of which patients should undergo a brain imaging study is pertinent.[10] Although such testing is of possible interest in all patients with a change in behavior, cost limitations are a reality, and some clinical guidelines are helpful. We recommend that any patient 40 years of age or older with an unequivocal change in neurobehavioral status, cognitive or emotional, should have a CT or MRI scan of the brain (Table 2). Applying this criterion clearly led to the detection of neoplasms in patients 2, 3, 7, and 8. Patient 6, with a 20-year history of depression but a new onset of mania at age 56, also illustrates this point. Primary psychiatric disorders such as schizophrenia and bipolar disorder typically begin in adolescence or young adulthood,[11] and the decision to scan the brain of a person younger than 40 can be made on an individual basis. The presence of symptoms and signs such as headache, nausea and vomiting, papilledema, seizures, and focal deficits clearly helps in this regard (Table 2). In our series, most patients were older than 40, and the two younger ones who might have had

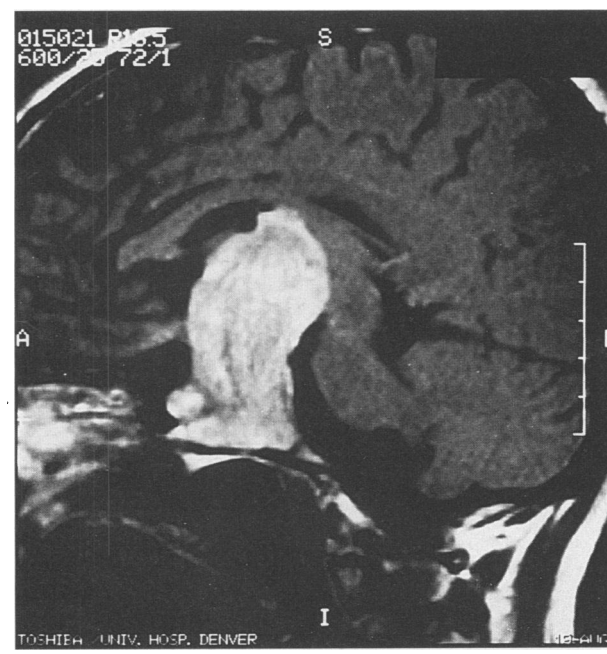

Figure 8.—*Temporolimbic tumor.* Patient 8 was amnesic for a year before this T1-weighted, enhanced sagittal magnetic resonance imaging scan disclosed a pituitary macroadenoma that upwardly displaced the forniceal columns and thalami (TR = 600 msec, TE = 25 msec). Debulking yielded substantial improvement in her memory.

schizophrenia (patients 4 and 5) had neurobehavioral or neurologic features (amnesia, anomia, hemiparesis) that distinguished them from patients with primary psychiatric illness. Another feature that implies the need for scanning is unresponsiveness to appropriate pharmacologic treatment of presumed psychiatric illness, as was the case in patient 1.

Clinical-Anatomic Correlations

Any lesion that destroys or disturbs a region of the brain can be expected to have an effect on a person's functioning, be it motor, sensory, or neurobehavioral. Neoplasms, however, pose some difficulties for examining clinical-anatomic correlations. Unlike cerebrovascular lesions, neoplasms may not be confined to discrete areas of the brain, and therefore, a precise correlation of lesion location and behavioral change is often not possible. Particularly with infiltrating gliomas, the possibility of associated edema, mass effect, and hydrocephalus and the progressive growth of the neoplasm can complicate these clinical-anatomic relationships. Neurobehavioral features and focal neurologic deficits can, however, be helpful in localizing the site of the neoplasm. Moreover, the introduction of CT and especially the more sensitive MRI has greatly improved the localization of brain tumors and permitted better clinical-anatomic correlation.

All eight cases presented with clinical features suggesting psychiatric dysfunction. Neuropsychiatric disturbances are more frequently associated with frontal and temporolimbic lesions and rarely with tumors in the parietal or occipital lobes.[4,7,12] The frontal lobes are the largest and phylogenetically most recent lobes of the human brain, and they play a central role in the organization and integration of behavior.[13] Three types of "frontal lobe syndrome" are recognized, based on the precise location of frontal lobe lesions: a dorsolateral syndrome that produces deficits in the organization and planning of behavior (executive function), an orbitofrontal syndrome with prominent disinhibition, and a medial-frontal syndrome with apathy or abulia.[14] All of these changes are more dramatic with bilateral than with unilateral frontal lobe involvement. In practice, these profiles often merge due to the widespread nature of many frontal lobe tumors. Patients 1 and 2 showed neurobehavioral changes consistent with bilateral medial-frontal involvement. Patient 3 had depression, another syndrome associated with frontal lobe damage.[14]

TABLE 1.—*Neurobehavioral Correlates of Neoplasm Location*

Patient	Tumor	Loation	Presentation
		Frontal Lobe Tumors	
1.....	Meningioma, transitional subtype	Bilateral medial frontal lobe	Abulia
2.....	Malignant primary immunoblastic lymphoma	Bilateral medial frontal lobe	Personality change
3.....	Metastatic squamous cell carcinoma of lung	Right frontal lobe	Depression
		Temporolimbic Tumors	
4.....	Oligoastrocytoma, grade I of IV	Left temporal lobe	Auditory hallucinations
5.....	Oligodendroglioma, grade II of IV	Right temporal lobe with massive edema	Auditory and visual hallucinations
6.....	Glioblastoma multiforme	Massive bilateral temporolimbic involvement	Mania
7.....	Pituitary adenoma, weakly gonadotrophic	Left temporal lobe with pressure on right parahippocampal gyrus	Panic attacks
8.....	Pituitary adenoma, weakly gonadotrophic	Thalami with displacement of forniceal columns	Amnesia

TABLE 2.—*Indications for Neuroradiologic Evaluation of Patients With Psychiatric Presentations*

Age ≥ 40 yr	Any new onset of cognitive or emotional dysfunction Unresponsiveness to appropriate drug treatment of presumed psychiatric disease
Comment: MRI and CT are roughly equivalent in detecting metastases, high-grade gliomas, and meningiomas that are common in this older age group; CT is particularly indicated when cost, facility access, pacemaker, cranial metal, agitation, claustrophobia, or back or arthritis pains preclude MRI scanning	
Age < 40 yr	Any new onset of cognitive or emotional dysfunction if associated with headache, nausea and vomiting, papilledema, seizures, or focal deficits Unresponsiveness to appropriate drug treatment of presumed psychiatric disease
Comment: MRI is preferable to CT because it more accurately detects low-grade astrocytomas and oligodendrogliomas, which tend to occur in this age group	

CT = computed tomography, MRI = magnetic resonance imaging

Temporolimbic tumors tend to cause psychosis due to the disruption of limbic system structures,[1,2,4,12] including components of the Papez circuit: the hippocampus, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nucleus, cingulate gyrus, and parahippocampal gyrus.[15] As is true of frontal lobe lesions, bilateral temporolimbic damage is more likely to cause these clinical manifestations.[16] In younger patients, neuropsychiatric manifestations are commonly due to primary psychiatric diseases, and those with brain tumors need, in particular, to be distinguished from patients with schizophrenia. Recent research has suggested a distinction between two varieties of schizophrenia; one with prominently "negative" features of apathy and social withdrawal, and the other with "positive" features such as delusions and hallucinations.[17] Positron emission tomography (PET) studies have shown decreased metabolic activity in the frontal lobes of schizophrenic patients with negative features,[17] and left temporal cortical volume loss has recently been demonstrated using quantitative MRI in patients with schizophrenia with positive features.[18] Whereas patients 1, 2, and 3 had presentations similar to those of schizophrenia with nega-

tive features, patients 4 and 5, with their prominent hallucinations, closely resembled those with schizophrenia with positive features. One of the most important distinctions between brain tumors and schizophrenia, however, is age. Schizophrenia rarely begins after age 40, and most schizophrenic patients are first seen between the ages of 15 and 25. In contrast, a new onset of primary or metastatic brain tumors is uncommon in this age range.

Mania is a disorder of mood and affect also associated with temporal lobe lesions, often right-sided.[19] Patient 6 had a unipolar depression without mania for many years, and the abrupt onset of her mania was more likely due to the bitemporal neoplasm than to a bipolar psychiatric disorder. Because of the extensive size and malignancy of her tumor, the prognosis was poor.

Panic attacks were initially noted in patient 7, who had a left temporal lobe lesion compressing the right medial temporal lobe. The right parahippocampal gyrus is a region recently implicated in panic attacks by PET studies.[20] Although another case of a pituitary adenoma causing panic attacks has been reported in the literature,[21] this case also had contributing factors from endocrinologic disturbance associated with Cushing's disease, and no compression of the parahippocampal gyrus was present. Patient 7 had a gonadotropic cell adenoma, and the panic attacks were most likely due to structural rather than endocrinologic abnormalities. A structural cause is supported by the fact that the panic attacks resolved after the tumor was debulked.

Memory loss was prominent in patient 8, emphasizing that amnesia is strongly associated with lesions of the temporolimbic regions, particularly the hippocampus and its connections.[22] Endocrinologic disturbances associated with this gonadotropic cell pituitary adenoma were not thought to be contributory. In this case, the thalamic involvement and displacement of the forniceal columns by the large midline pituitary adenoma likely caused the amnesia, which improved after surgical therapy.

Conclusion

In summary, we report the cases of eight patients with frontal or temporolimbic tumors who presented psychiatrically but whose age of onset, associated features, or unresponsiveness to appropriate pharmacologic therapy suggested a structural lesion. We advocate brain imaging in patients 40 years of age or older who have the onset of cognitive or emotional dysfunction and in any patient with such a presentation who has additional neurobehavioral or neurologic features or a poor response to appropriate psychopharmacologic treatment. This series of cases highlights the importance of searching for possibly curable neoplasms that might otherwise go undetected. These cases also emphasize the importance of frontal and temporolimbic systems in the pathogenesis of neurobehavioral disorders.

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